



NOTES

TRINUCLEOTIDE REPEAT EXPANSION DISEASES

GENERALLY, WHAT ARE THEY?

PATHOLOGY & CAUSES

- Group of genetic diseases; mutations characterized by increased number of 3 base pair repeats
 - C, G *nucleotides*: loci at which repeats expanded
- Mechanism of disease
 - *Loss-of-function*: transcriptional silencing
 - *Toxic, gain-of-function*: may occur at mRNA, translational level/protein structure level

RISK FACTORS

- Family history

COMPLICATIONS

- Anticipation
 - More severe, earlier-onset of disease as mutation passed down

SIGNS & SYMPTOMS

- See individual diseases

DIAGNOSIS

LAB RESULTS

- Genetic testing for number of repeats

OTHER DIAGNOSTICS

- Family history, physical examination (disease-specific, pathognomonic findings)

TREATMENT

OTHER INTERVENTIONS

- No curative treatment currently available
- Symptom management (hallmark of therapy)

FRAGILE X SYNDROME

osms.it/fragile-x-syndrome

PATHOLOGY & CAUSES

- Autosomal recessive, X-linked disease; *intellectual disability*, typical facies, macroorchidism
- Inherited defect in 5' untranslated region (UTR) of familial mental retardation-1 (*FMR1*) gene → *trinucleotide expansion* → abnormal length → ↑ *methylation* → promoter region methylation → ↓ transcription of *FMR1* gene → ↓ familial mental retardation protein (*FMRP*) *synthesis* → clinical phenotype

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FMRP

- High concentration in testes, brain
- mRNA transport protein
 - ↓ FMRP → ↓ transport of neuronal proteins from perinuclear space → dendritic spines → dysregulated synaptic function
- Translation regulator
 - ↓ FMRP → via ↑ metabotropic glutamate receptor activity → ↑ translation of bound mRNA at synaptic junction → dysregulated synaptic activity → intellectual disability

CAUSES**Trinucleotide (CGG) repeat expansion**

- Trinucleotide (CGG) repeat expansion on 5' UTR *FMR1* gene at Xq27.3 locus
 - 45–54: intermediate expansion repeat number
 - 55–200: carrier/premutation individual repeat number
 - 200–4,000: affected individual repeat number

Inheritance

- Autosomal recessive (some caveats)
- Mutations occur/worsen during oogenesis, not spermatogenesis → abnormal autosomal recessive expression
 - 20% of disease-genotype individuals who are biologically male: asymptomatic, carriers
 - 30–50% of genotypically carrier individuals who are biologically female: symptomatic (preferential X-chromosome inactivation → inconsistent mutation expression → variable symptom presentation)
- Anticipation
 - Genetic mutations continue through pedigree → ↑ length of expansion → ↑ severity of disease

RISK FACTORS

- Genotype-phenotype correlation
 - Repeat size, methylation mosaicism: ↑ % cells with same expression/methylation amount → ↑ phenotype penetrance

COMPLICATIONS**Behavioral features**

- Autism, attention-deficit hyperactivity disorder (ADHD), anxiety disorders

Seizures

- Simple/complex; occurs commonly in childhood, resolves in adulthood

Fragile X tremor/ataxia

- Observed in carrier/premutation individuals
- Tremor/ataxia → parkinsonism
 - Short-term memory loss, executive dysfunction (common)
 - Individuals who are biologically female: ovarian insufficiency; early menopause (age ≤ 40)
- Pathogenesis
 - Mild CGG repeat expansion → mild ↑ methylation (not including promoter region) → adequate transcription → RNA product → poor translation → abnormal protein → nuclear accumulation → aggregation of mRNA-binding protein → toxic effects to cell function → neurodegeneration

SIGNS & SYMPTOMS**Impaired cognitive function**

- Developmental delay: delayed attainment of language, motor milestones
 - Delayed milestones: sit alone (10 months), walk (18 months), clear spoken words (20 months)
- Intellectual disability: IQ range of 20–60

Physical features

- Prominent in adulthood; more common in individuals who are biologically male
- Facies
 - Prominent forehead, jaw; long, narrow face; large ears
- Macroorchidism
- Connective tissue
 - Joint hyperlaxity, arched palate, flat feet, mitral valve prolapse (benign)
- Behavioral features
 - Hyperactivity, inattention, gaze aversion, stereotypic movements (e.g. hand-flapping, unusual speech patterns)



Figure 28.1 A child with fragile X syndrome.

DIAGNOSIS

LAB RESULTS

DNA testing (obtained prenatally)

- Chorionic villus sampling (11–13 weeks of gestation)
 - Degree of methylation variable in later development
- Amniocentesis (> 15 weeks of gestation)

Complete prenatal screening

- DNA testing
- Fluorescent polymerase chain reaction (PCR)
 - Identify degree of methylation
- AGG trinucleotide genotyping
 - Determine risk in premutation/carrier expansion individuals who are biologically female

OTHER DIAGNOSTICS

History

Physical examination

- Phenotypic characteristics on musculoskeletal, genitourinary examination
- Neurological
 - Mental status (intellectual, behavioral deficits)

TREATMENT

MEDICATIONS

- Symptom-directed management

Behavioral features

- ADHD presentation
 - < 5 years old: non-stimulant therapy (e.g. guanfacine, clonidine)
 - > 5 year old: stimulant prescription (e.g. methylphenidate)

Anxiety/mood disorders

- Selective serotonin reuptake inhibitors (SSRIs)

Seizures

- Anticonvulsants

Premature ovarian insufficiency

- Estrogen replacement therapy

PSYCHOTHERAPY

- Symptom-directed management

Behavioral features

- Counseling, psychotherapy

OTHER INTERVENTIONS

- No curative therapy

Symptom-directed management

- Intellectual disability
 - Speech/language therapy, early intervention, special education

Prevention

- Genetic preconception counseling
 - Preconception reproductive options (e.g. use of donor gametes from unaffected donor)

HUNTINGTON'S DISEASE

osms.it/huntingtons-disease

PATHOLOGY & CAUSES

- Autosomal dominant, neurodegenerative disease; chorea, dementia
 - Average age of onset is 40
- Medium spiny striatal (GABAergic) neuronal cell death → dysregulation of basal ganglia circuitry → unchecked dopamine, glutamate-mediated basal ganglia activity → ↑ motor output → hyperkinetic movement
- Cortical cell death → cognitive impairment

CAUSES

Trinucleotide repeat (CAG) expansion

- Trinucleotide repeat (CAG) expansion of first exon in **huntingtin (HTT) gene on chromosome 4p16.3**
 - **Intermediate repeat number:** 27–35 (rarely causes disease)
 - **Disease repeat number:** 36–39 (incomplete penetrance)
 - **Disease repeat numbers:** > 40 (complete penetrance ↑ repeat number → ↓ age of onset)
- **Repeat CAG expansion** in first exon of HTT → expansion of polyglutamine region at N terminus of HTT protein → gain-of-function
- Physiologic role of HTT protein unknown (high levels found in brain tissue)

Possible pathophysiologic roles of HTT protein

- Aggregation of protein → cellular dysfunction
 - Aggregation → uptake by neurons → neuronal death; akin to prion-like pathogenesis; most prominent aggregation (neuronal death) in caudate, putamen (AKA neostriatum)
 - Aggregation → ↑ proteasomal, autophagic degradation pathways → dysregulated cell injury, death
- Transcriptional dysregulation

- Abnormal HTT protein → binding of various transcriptional regulators → ↓ mitochondrial oxidative stress protective genes → susceptibility of oxidative damage → neuronal death

- Altered levels of brain-derived neurotrophic factors

Role of ras homolog enriched in striatum (Rhes)

- Avidly bind with mutant huntingtin
- Protein selectively expressed in striatum
- Rhes → mediates covalent attachment of small ubiquitin-like modifier (SUMO) to HTT → ↑ HTT aggregation → neurotoxicity

Inheritance

- **Autosomal dominant**
- **Anticipation**
 - Repeat expansion occurs during spermatogenesis → paternal transmission associated with early age of onset

COMPLICATIONS

- Depression → suicide
- Dysphagia → aspiration pneumonia (common cause of death)

SIGNS & SYMPTOMS

- Motor symptoms (movement inhibition; excessive, involuntary movements)
 - Hypotonia with hyperreflexia (early symptom), **chorea** (e.g. face, head, neck, tongue, trunk, extremities), **athetosis**, dystonia, eye movement slows, gait abnormalities (unsteady, irregular → bradykinesia, rigidity in late disease)
- Psychiatric
 - Apathy, irritability, **depression**, delusions, **aggression**, disinhibition, paranoia

- Cognitive
 - Progressive **dementia**, inflexibility of thought; ↓ insight, concentration; memory loss
- Weight loss, cachexia

DIAGNOSIS

DIAGNOSTIC IMAGING

MRI

- Atrophy of head of **caudate** nuclei

LAB RESULTS

- Genetic testing for CAG repeat in HTT (> 36 repeats)

OTHER DIAGNOSTICS

- History
- Physical examination
- Neurological
 - Motor, mental status examination

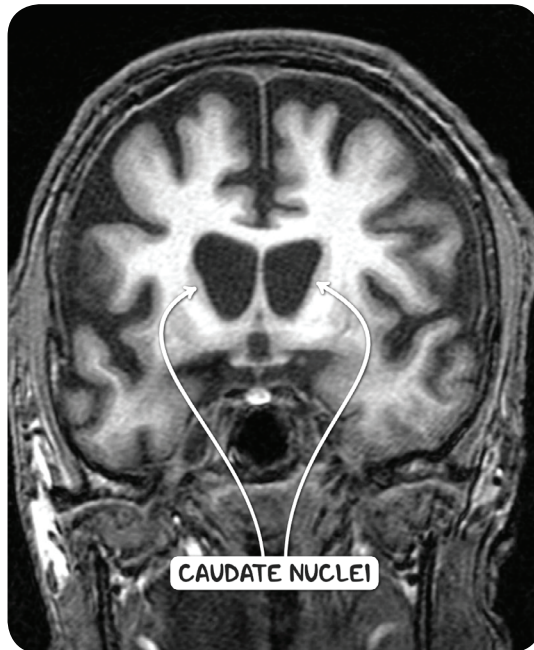


Figure 28.2 An MRI scan in the coronal plane of the head of an individual with Huntington's disease. There is atrophy of both caudate nuclei which has led to hydrocephalus ex vacuo. There is also generalized cortical atrophy.

TREATMENT

MEDICATIONS

Chorea (symptomatic therapy)

- Presynaptic VMAT2 (vesicular monoamine transporter Type II) inhibitors: tetrabenazine/deutetrabenazine
 - ↑ synaptic metabolism of dopamine → ↓ dopamine → ↓ basal ganglia output → ↓ hyperkinetic output
 - May exacerbate parkinsonism symptoms
 - As late symptom (e.g. chorea abates), periodic review of dosing recommended
- Neuroleptics: **haloperidol/chlorpromazine**
 - Dopamine receptor antagonists → ↓ dopaminergic input → ↓ basal ganglia output → ↓ hyperkinetic output
 - Similar parkinsonism side effects/exacerbation of symptoms
- Psychosis: quetiapine (dopamine, serotonin antagonist properties)

PSYCHOTHERAPY

- Chorea (symptomatic therapy)
 - Counseling, techniques to ↓ anxiety, stress

OTHER INTERVENTIONS

- No curative therapy
 - Palliative, advance care planning
- Symptomatic therapy
 - Chorea (severe cases): assistive equipment (e.g. helmets, padded reclining chairs, low beds)
 - Dysphagia: thickened liquids
 - Speech, language problems: physical therapy
 - Gait impairment: hip protectors → ↓ hip fractures → ↓ morbidity